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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,897	03/09/2006	Andrew James Culshaw	PN/4-32697A	2416

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
TRUONG, TAMTHOM NGO	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,897	CULSHAW ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4-11-05 (Pre. Amdt.)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,12 and 13* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,12 and 13* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-11-05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL ACTION

Applicant's preliminary amendment of 4-11-05 is acknowledged

Claims 7, 8, 10 and 11 are cancelled.

Claims 1-6, 9, 12 and 13 are pending.

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-4, 6 (in part), 9, 12 and 13, drawn to compounds of formula I and pharmaceutical composition thereof, first process of making said compounds and method of treating a disease related to vanilloid receptor.

Group II, claim(s) 5, drawn to a compound of formula II .

Group III, claim 6 (in part), drawn to the second process of making same compounds of formula I.

The invention listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: They relate to compounds of considerable structural dissimilarity as the quinazoline core is absent in group II. The substituents at R^1 in the

two groups are not coextensive as the scope is broader for II and thus it cannot be said that the compounds within I-II share a special technical feature.

In accord with 35 USC 121 and 372, applicants are advised that where **more than one process** of making is claimed along with compounds, the first recited process is considered to form part of the main invention. See 37 CFR 1.475(d). Thus only the first process in claim 6 is being examined.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims **will be fully examined for patentability in accordance with 37 CFR 1.104**. Thus, to be allowable, **the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112.** Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained.

Withdrawn method claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the method claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

During a telephone conversation with Mr. Peter J. Waibel on 5-24-07 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-4, 6, 9, 12 and 13. Affirmation of this election must be made by applicant in replying to this Office action. Claim 5 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Scope of Enablement (on scope of treatment):** Claims 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of **treating** chronic pain and neuropathic pain, **does not** reasonably provide enablement for a method of treating much less preventing other diseases urged treatable based on vanilloid receptor (or VR1) activation such as: inflammatory airways disease, Crohn's disease, ulcerative colitis, pancreatitis, inflammatory skin disorder, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 12 recites: "A method for treating or preventing a disease or condition in which vanilloid receptor activation plays a role or is implicated...." Said method covers the treatment of several diseases such as:

> **[0070]** In view of the above, the agent of the invention are useful in the prevention and treatment of diseases and conditions in which human VR1 activation plays a role or is implicated. Such conditions include in particular chronic pain, i.e. for the treatment of hyperalgesia and, in particular, for the treatment of severe chronic pain; neuropathic pain associated with postherpetic neuralgia, amputations ("phantom limb pain"), reflex sympathetic dystrophy and other chronic nerve injuries; inflammatory pain, e.g. chronic inflammatory pain, bone and joint pain (osteoarthritis), cancer pain, myofascial pain (muscular injury, fibromyalgia) and perioperative pain (general surgery, e.g. associated with burns, sprains, fracture or the like, subsequent to surgical intervention, gynecologic surgery); or in asthma, for example, aluminosis, anthracosis, inflammatory diseases for example inflammatory airways disease, e.g. Chronic Obstructive Pulmonary Disease; asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis, and rhinitis; smooth muscle relaxants, e.g. for the treatment of spasm of the gastro-intestinal tract or uterus, e.g. in the therapy of Crohn's disease, ulcerative colitis or pancreatitis, inflammatory bowel disease, cystitis, e.g. interstitial cystitis, pancreatitis, and uveitis; inflammatory skin disorders and rheumatoid arthritis, inflammatory skin disorders, for example psoriasis and eczema.

Many of the cited diseases have different symptoms and manifestation, and thus, the scope of the above claims is unduly broad. See MPEP 2164.01 (c).

Claim 13 is a claim of pharmaceutical composition but recites the intended use of treating or preventing a disease related to vanilloid receptor, which is unduly broad.

The amount of direction or guidance presented: The specification describes two *in-vitro* assays. One of them is for the interaction of vanilloid receptor with the claimed compounds. The other is a an assay for the anti-hyperalgesic effects. Clearly, the focus is mainly on the treatment of chronic pain and neuropathic pain. There is no evidence if this compound could be a bronchodilator, or treating inflammatory airways disease, Crohn's disease, ulcerative colitis, pancreatitis, inflammatory skin disorder, etc Thus, the specification does not provide sufficient enablement for the treatment of other diseases related to vanilloid receptor.

The state of the art: Typically, compounds with the core of 3H-quinazolin-4-one are known to antagonize angiotensin II (AII) as evident by the teaching of **Levin et. al.** (US 5,284,853), **Venkatesan et. al.** (US 5,294,617), **Crandall** (US 5,830,909). Thus, this type of compounds is not known to treat pain much less treating any disease related to vanilloid receptor. Therefore, the state of the art does not support the broad scope of treatment recited in claim 12, and the intended use in claimd 13.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula I. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound.

Given a large Markush group of the claimed formula I, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the assays shown the specification can only substantiate using compounds of the instant formula (I) in the treatment of chronic pain or neuropathic pain, and not any other diseases related to vanilloid receptor.

See ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Thus, with such a limited teaching, the skilled clinician would have to carry out undue experimentation to use the claimed compounds in the methods recited in the above claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by **Bhattacharya et. al.** (WO 97/ 28118).

On page 19, Table 1, **Bhattacharya et. al.** lists compound #19 which reads on the instant formula I with the following substituents:

i. R_1 is halogen;

ii. R_1 is halogen;

iii. R_3 is alkyl.

Note, claim 13 does not have a proviso as in claim 1, and the intended use does not have patentable weight. Since the disclosed compound has a pharmaceutical use, then its composition is inherently taught.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 9 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Bhattacharya et. al.** (WO 97/28118). In Table 1, **Bhattacharya et. al.** teaches many quinazolinone compounds for antagonizing AII, inhibiting ACE, ... etc. Note, compound #19 (in Table 1) has been excluded; however, other compounds show substituents of *alkyl, alkoxy, halogen* at the 7-position (corresponding to the instant R^2) as well. Thus, the generic definition of the reference's R^2 and R^3 (page 8, lines 9-10) allows for mixed halogens (e.g., I/Cl, Cl/Br, etc.), which are not excluded by the proviso as well as the alkyl/halogen combination.

Thus, with the equivalency teaching provided and species showing *halogen* at the 6- or 7-position as well as an alkyl group at 7-position, the skilled chemist would have been motivated to make a compound of the instant formula I because one would have expected such a compound to be AII antagonist, or ACE inhibitor, etc.

Thus, at the time of the invention, it would have been obvious to make the instant quinazolinone compound in view of the teaching above.

Claim Objections

4. Claim 6 is objected to for reciting a non-elected second process. The prior arts of record do not read on the first process of claim 6 in which $C{=}N\text{-}R^3$ is a starting material.

Information Disclosure Statement

The IDS of 4-11-05 has only been considered in part. The reference of **El-Sharief** is not provided. Applicants are request to submit a copy of said reference for consideration.

Applicants are requested to state the reason(s) for the remaining provisos and to identify art which may have necessitated such.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Tamthom N. Truong
Examiner
Art Unit 1624

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5-28-07

EMILY BERNHARDT
PRIMARY EXAMINER
GROUP 1600